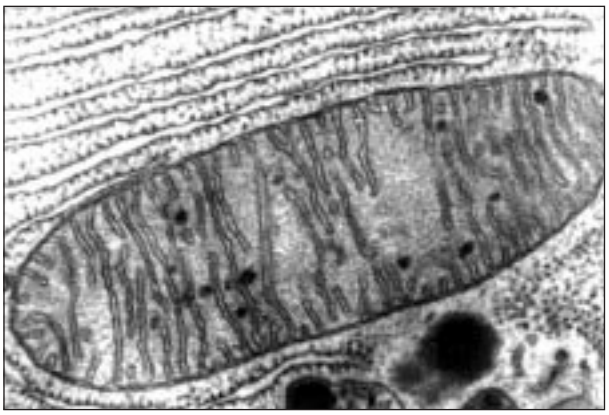
Stress on tiny cell component has dire consequences

Various life sustaining metabolic processes of animals and humans are powered by energy converted from food and oxygen by mitochondria. A complex cycle converts glucose and oxygen into the energy required by cells. Mitochondria, tiny organelles in cells, have their own DNA, most of which is inherited from the mother.



Mitochondria

Mutations in mitochondrial DNA are either passed from mother to child or they may also occur somatically during the early life of the animals. Within the organelle there are many copies of the DNA so a mutation may remain dormant because there are many mitochondria within a cell. However, over time mutated DNA gets enriched due to various biochemical factors. Mutations in mitochondrial DNA also occur due to external influences like chemicals, drugs, radiation, and the like, and they become cumulative as the animal or human ages. When mutations interfere with the proper function of the mitochondria disease results.

Dr. Narayan Avadhani, Harriet Ellison Woodward Professor of Biochemistry at the School, studies mitochondria. Currently he and his group are examining the effects of stress, caused by interruption of the function of the organelle. It has been known for a number of years that mitochondrial DNA is the direct and preferential target of attack by varied carcinogens, which cause mutations to the DNA. The mutations accumulate and eventually interfere with the oxygen utilization and energy production. Recent work in Dr. Avadhani's laboratory also showed that mitochondrial DNA or membrane damage also triggers a stress response cascade through the altered cellular Ca^{2+} (calcium ions) pool that causes a major change in the expression of nuclear genes and cell morphology.

While investigating mitochondria-to-nucleus stress signaling, the group found that some of the genes implicated in tumor progression are activated and overexpressed in otherwise non-malignant cells when mitochondria are stressed. The chemistry within the organelle and hence in the whole cell is changed as a result of mitochondrial stress signaling. A change in mitochondrial membrane property and reduced energy production in some cells of a tumor mass leads to increased intracellular calcium. This in turn leads to the activation of genes that make cells more invasive or metastatic. Such cells show increased resistance to apoptosis (cell death) and keep proliferating. The study shows the existence of a new pathway for cancer progression, which is activated as part of the mitochondrial genetic and metabolic stress signaling. The researchers found that reversal of the mitochondrial stress in these tumor cells also partly reversed the mitochondrial stress-induced phenotypic changes and invasive behavior.

"The stress signaling may therefore be a critical factor in the ability of some cells within a tumor mass to acquire invasive phenotypes and undergo morphological changes leading to tumor progression and metastasis," explains Dr. Avhadhani. "In summary, mitochondrial dysfunction and the resulting alterations in nuclear gene expression through mitochondria-to-nucleus stress signaling might be an important factor in cancer progression and tumor cell metastasis."

NIH/Merck Summer student research program

Veterinarians play an important role in all aspects of biomedical research, in industry, government agencies and academia. To encourage students to consider research as a career, the School, in 1990, initiated a summer student research program with a grant from the Merck Foundation, supplemented by School funds. That year, six students participated in the program. Now the program receives support from NIH and Merck and the number of students who received grants in the summer of 2002 grew to 17.

Students receive a stipend and gain research experience in all phases of biomedical research. They work in the laboratories of clinical and basic researchers at the School as well as at other locations within the University.

The program enables students to perform research full time during June, July and August and participate in weekly seminars as well as a national meeting in August. Students make short oral presentation to peers and write a paper at the end of the summer that is submitted to the School's Phi Zeta Day.

The program, under the direction of Dr. Michael Atchison, professor of biochemistry and director of the V.M.D./Ph.D. program, in 2002 generated such diverse research projects as those studying detailed molecular-biological mechanisms of growth control, to studies on the dynamics of West Nile Virus infection in the United States. The caliber of the research performed was outstanding and the application pool continues to grow each year. Since inception of the program, over 20 research papers and 11 meeting abstracts have been published. Considering the short training period, this is an excellent level of productivity.

Since the inception of the program, 156 awards have been funded for 136 students (some students participate more than once). Many of the students pursue research careers after graduation. The current positions of 47 recent graduates (1998-2001) show that 32% are pursuing post-graduate education (postdoc, graduate program, residency, internship), 57% are in clinical practice, 2% other and the pursuits of 9% are unknown. Looking further back to students at least five years out of the program (1990-1997), current positions are distributed as follows: 12% academic faculty, 14% post graduate education (postdoc, graduate program, residency, internship), 57% in clinical practice 5% industry, 5% other, 7% unknown pursuits.

Continued funding is expected for the program in 2003 since Merck Foundation funding has been continuous over the past 13 years and the NIH competitive renewal grant received an outstanding score. Dr. Atchison hopes for even more applicants and awards than in 2002.